REMARKS

Claims 13-34 are in the case. Claims 13, 14, 17, 18, 20 and 21 have been amended and claims 25-34 have been added. Claims 25-29 find support in original claims 14, 17, 18, 20 and 21, which have been amended to clarify their scope and not for reasons related to patentability. Support for claims 30-34 is found, e.g., at p. 3, line 18 - p. 4, line 7 of Applicant's specification.

In one aspect, recited in amended claim 13, Applicant's invention features a method of prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma. The method includes instructing a patient to inhale, as needed for short-term symptomatic relief of asthma symptoms, an effective amount of a composition containing an admixture of (a) budesonide and (b) formoterol or a formoterol salt and/or solvate, referred to below as "a budesonide/formoterol composition,".

Asthma is a chronic inflammatory disease of the airways. Persistent asthma requires daily long-term therapy in addition to appropriate medications to manage asthma exacerbations (commonly referred to as "asthma attacks"). (See, e.g., "*Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma*," NIH Publication No. 97-4051.)

Asthma medications are categorized into two general classes: (a) long-term control medications, which are taken daily on a long-term basis to achieve and maintain control of persistent asthma (also known as long-term preventive, controller or maintenance medications), and (b) quick-relief medications, which are taken to provide prompt reversal of acute airflow obstruction and relief of accompanying bronchocontriction (also known as reliever or acute rescue medications). Patients with persistent asthma generally require both classes of medication. *Id.*

A clinician may initially prescribe only a quick-relief medication, such as a short-acting inhaled β2-agonist, e.g., salbutamol (albuterol) or terbutaline, for a patient who appears to have mild or intermittent asthma. Use of quick-relief medications on a daily basis, or increasing use, indicates the need for additional long-term therapy. While quick-relief medications are the drug of choice for treating acute asthma symptoms, regularly scheduled daily use of these medications is not generally recommended. (See, e.g., *supra*, pp. 64 and 67.)

Because inflammation is an early and persistent component of asthma, long-term therapy for persistent asthma should be directed toward long-term suppression of inflammation. Corticosteroids are the most potent and consistently effective long-term control medication for asthma.

While corticosteroids are generally effective in long-term suppression of inflammation, they are not to be used to treat acute symptoms or exacerbations. (See, e.g., *supra*, pp. 62 and 70, where a statement to this effect appears as a bold-face warning.) Corticosteroids are generally relatively slow acting, and may take 6 hours or more to produce a detectable effect. (See, e.g., Am J Med, 74 (1983), pp. 845-851.) Due to this time delay, corticosteroids have traditionally been considered unsuitable for acute therapy. At present, short-acting inhaled β2-agonists are the only medications that are recommended for use in acute therapy.

A newer β2-agonist, formoterol, has been shown both to have a rapid onset, comparable with other β2-agonists, and to be effective and well-tolerated as a maintenance treatment for patients who, despite optimal treatment with inhaled corticosteroids, continue to have nocturnal asthma or require frequent use of quick-relief medications. Formoterol has been recommended for use in later stages of an asthma maintenance schedule, i.e., on a maintenance basis for patients with relatively severe asthma. (See, e.g., *The British Guidelines on Asthma Management 1995 Review and Position Statement* (Thorax, 52, Suppl. 1, February 1997).)

When patients experience a period of increased symptoms, the current protocol is for the patient to be reassessed by a physician to determine whether the dosage of the patient's long-term control medication should be increased. This generally results in a delay before the patient can obtain more effective treatment, due to the patient's reluctance to contact the physician and/or the lapse of time before the physician can see the patient. This delay may cause the patient's asthma to worsen, and may even lead to a severe exacerbation which may require emergency room treatment.

It has been observed that symptoms and use of quick-acting medications consistently increase several days before the onset of a clinical exacerbation (Am J Respir Crit Care Med 160(2) (1999), 594-9).

The inventors have recognized that budesonide/formoterol compositions can be safely administered to asthma patients on an "as needed" basis. In other words, a physician can instruct

a patient to inhale one or more doses of a budesonide/formoterol composition whenever the patient is in need of short-term symptomatic relief of asthma symptoms. Because more frequent inhalation of such a composition will provide not only quick relief but also a reduction of inflammation, by prescribing this "as needed" treatment the physician allows the patient to self-adjust the dosing of corticosteroid. Thus, clinical reassessment is not required each time a period of more severe asthma is expected, reducing the delay-related problems discussed above.

Thus, the patient's symptoms guide the dose and dose frequency -- when the patient feels the need for more frequent use of quick-relief medication, as is often the case prior to the onset of an episode of more serious asthma, the patient will automatically receive more corticosteroid, which will provide long-term treatment of inflammation. Allowing the patient to easily self-regulate the dose of corticosteroid based on the patient's symptoms will tend to improve the patient's confidence level, by reducing the frequency of exacerbations. This increase in confidence may in turn lead to improved patient compliance.

The use of the budesonide/formoterol composition on an "as needed" basis is beneficial both for patients who are not on a regular maintenance program of corticosteroid treatment, and for patients who are receiving maintenance treatment. In the former case, patients will receive some long-term benefit without the need for a separate inhaler and daily inhalation regimen. In the latter case, the "as needed" treatment will tend to self-correct problems that result from a too low maintenance dose of corticosteroid.

Claims 13-15, 17-18 and 20-24 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Carling (WO 93/11773). Claims 16 and 19 have been rejected as being unpatentable over Carling in view of Hett et al. and Ryrefeldt et al.

Applicant respectfully requests that these rejections be withdrawn. There is no recognition in the Carling reference that the budesonide/formoterol compositions described therein would be suitable for use on an "as needed" basis, much less that their use in this manner would be advantageous. Instead, Carling states that "the intended dose regimen is a twice daily administration." This is in keeping with general clinical practice and many clinical guidelines, which recommend only short-acting inhaled β2-agonists for acute therapy, as discussed above.

The secondary references do not supply a teaching or suggestion of the use of budesonide/formoterol compositions on an "as needed" basis. Instead, these references are cited

to provide teachings that (R,R)-formoterol and the 22R epimer of budesonide are particularly potent forms of formoterol and budesonide.

Accordingly, Applicant respectfully submits that the claims are patentable over these references.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed is a check for a $110.00 for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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ersion with markings to show changes made

In the claims:

Claims 13, 14, 17, 18, 20 and 21 have been amended as follows:

13. A method of prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma[, when needed,] which comprises [administering, by inhalation, to]

instructing a patient to inhale, as needed for short-term symptomatic relief of asthma symptoms, an effective amount of a composition comprising, in admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient which is budesonide.

14. The method according to claim 13, wherein the molar ratio of (a) to (b) calculated as formoterol to budesonide is from 1:1 to 1:100[, preferably from 1:1 to 1:70].

17. The method according to claim 13, wherein a unit dose of formoterol lies in the range of from 1 μg to 48 μg[, preferably between 3 μg to 12 μg], calculated as formoterol fumarate dihydrate.

18. The method according to claim 13, wherein the daily dose of formoterol, including maintenance therapy, lies in the range of from 1 μg to 100 μg[, preferably from 2 μg to 60 μg], calculated as formoterol fumarate dihydrate.

20. The method according to claim 13, wherein a unit dose of budesonide lies in the range of from 20 μg to 1600 μg[, preferably between 50 μg to 400 μg].

21. The method according to claim 13, wherein the daily dose of budesonide, including maintenance therapy, lies in the range of from 20 μg to 4800 μg[, preferably from 30 μg to 3200 μg].